Methotrexate-induced nephrogenic diabetes insipidus: first case report

Sir, Methotrexate (MTX) has become the dominant second-line agent in the treatment of patients with rheumatoid arthritis (RA). Several studies have shown that MTX has a very good long-term safety profile, and renal toxicity is very rare [1, 2]. We report a case of renal toxicity induced by MTX that provides the first description of MTX-induced nephrogenic diabetes insipidus in a patient with RA.

A 39-yr-old male with no previous nephropathy and a 4-yr history of RA was receiving 12.5 mg MTX weekly and non-steroidal anti-inflammatory drugs (NSAIDs), with a very good clinical response. Six weeks after the initiation of MTX therapy, he experienced polydipsia, nocturia and polyuria (urine output around 9 l/day). The complete blood cell count, renal function (measured by plasma creatinine concentration and creatinine clearance) and sodium, urea and other solutes were within normal limits. Examination of the urine revealed no trace of proteins or cells but osmolality on the low normal range (140 mOsm/kg). Diabetes insipidus (DI) was then suspected and a standard fluid deprivation test was done. During 8 h of water deprivation, urine osmolality did not exceed 300 mOsm/kg. When antidiuretic hormone was given (5 units subcutaneously), urine osmolality increased by about 40% (increase of 38% after 4 h). Magnetic resonance imaging of the brain excluded pituitary abnormalities.

The diagnosis of partial nephrogenic DI was then suggested and NSAIDs were withdrawn. No clinical improvement was seen after 2 weeks, and therefore MTX was also stopped. Seven days after MTX withdrawal, polydipsia and polyuria disappeared and urinary osmolality normalized.

Three years later, MTX was reintroduced in association with low-dose corticosteroids. The polyuria, nocturia and polydipsia returned but disappeared when MTX was withdrawn.

MTX has virtually no renal toxicity, although it may cause a mild decrease in glomerular filtration rate and tubular secretion [3]. This is why MTX is the drug of choice for combining with other therapeutic agents. However, our knowledge of the toxicity profile of MTX is still being refined, as new toxic effects continue to come to light even after five decades of the use of this drug [2].

Drug-induced nephrogenic DI is a well-recognized side-effect of several therapies, but it is rarely found when cytotoxic drugs are used [4, 5]. To our knowledge, there is no evidence of nephrogenic DI when MTX is used at typical anti-rheumatic doses (7.5–15 mg weekly). The present case throws no light on the mechanism by which MTX might cause such an effect. However, this report may contribute to our knowledge of the safety profile of MTX.

M. C. Fernández-Espartero, M. Rodríguez, J. de la Mata
Rheumatology Unit, Hospital de la Zarzuela, Pléyades, 25 Aravaca, 28023 Madrid, Spain

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Correspondence to: J. de la Mata.